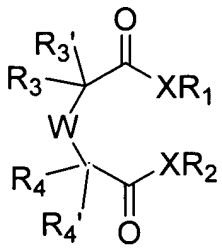
REMARKS

Claim 1 has been amended, support for the amendment can be found in Claim 19. Claim 19 has been amended, support for the amendment can be found in Claim 55. Claim 23 has been amended to correct the dependency of the claim. Claim 28 has been amended to correct a minor informality. No new matter has been introduced by this amendment. Claims 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-53, 55 and 58 remain pending. The following addresses the substance of the Office Action.

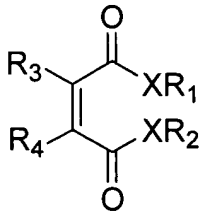
Rejection under 35 U.S.C. §112

The Examiner has maintained rejection of Claim 30 under 35 U.S.C. §112, first paragraph, for allegedly lacking written description. More specifically, the Examiner indicated that Claim 30 was rejected because the specification does not describe the structure of the endogenous inducer of dendritic cell migration and maturation. The Examiner cited the Lilly and Enzo cases in support for this rejection. Applicant respectfully disagrees for the following reasons.

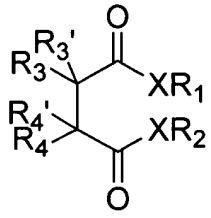
The Federal Circuit in Lilly stated that "a written description of an invention involving a chemical genus, like a description of chemical species, requires precise definition, such as structure, formula or chemical name of the claimed subject matter to distinguish it from other materials" (emphasis ours). Claim 30 is not claiming the endogenous inducer of dendritic cell migration and maturation. Instead, the subject matter claimed in Claim 30 is method of vaccinating a mammal, comprising *inter alia* the steps of introducing into the mammal an effective dose of the antigen or an epitope(s) thereof; and administering to the mammal a topical treatment..., wherein the topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and in the absence of an antigen inducing dendritic cells to migrate to the draining lymphoid organ, and wherein said lipophilic molecule is ≤500 daltons and is selected from the following formulas:



(1)



(2)



(3)

wherein R_1 and R_2 are independently... wherein the amount of topical treatment is further characterized as being sufficient to increase local release of an endogenous inducer of dendritic cell migration and maturation" (emphasis added). Here, the chemical genus of the topical treatment recited in Claim 30 is clearly described in the specification with sufficient precision, including chemical structure, to satisfy the written description requirement. The "endogenous inducer" is recited in Claim 30, as a functional limitation on the amount of the topical treatment to be administered. It is not a claimed chemical genus—it is a class of well known specific cytokines. Indeed, the specification provides a list (GM-CSF, IL-1a, TNF-a, MIP-1a, IL-4, etc.) of such endogenous inducers of dendritic cell migration and maturation. The structural and functional characteristics of the listed inducers are well known to those of skill in the art (see e.g., the cited references in the excerpt below). See in the specification, page 24, lines 18-28, stating:

> "...cytokines and chemokines... modulate Langerhans cell migration and maturation. For instance, granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-1a (IL-1a) may mediate *in vitro* maturation (Larregina et al. 1996 Immunology 87:317-325). Tumor necrosis factor-a (TNF-a) is involved in Langehans cell migration (Banchereau and Steinman 1998 Nature 392:245). Other factors implicated in the control of various aspects of Langerhans cell maturation and/or migration include MIP-1a, IL-4, G-protein-coupled receptors for the calcitonin-gene related peptide, C5a and other chemokines (Banchereau and Steinman 1998 Nature 392:245)."

No reasonable reading of Lilly or Enzo requires that substances, like the disclosed cytokines and chemokines, must be defined in precise structural terms, where those of skill in the art are well aware of their structures and functions. Unlike the claims at issue in Lilly and Enzo (which recited compositions, cDNA in Lilly and DNA probes in Enzo), here Applicant is not claiming the endogenous inducers. Instead, Applicant is claiming a method, in which the dose of

administered substance (topical treatment) is defined as being sufficient to increase the local release of an endogenous inducer (known cytokines and chemokines described in the specification).

Moreover, under the MPEP 2163 standard, "[a]n adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention" (emphasis added). Here, as discussed above, the skilled person would understand from the claim language ("wherein the amount of topical treatment is further characterized as being sufficient to increase local release of an endogenous inducer...") and the supporting written description (examples of endogenous inducers include GM-CSF, IL-1a, TNF-a, MIP-1a, IL-4, etc.) that the inventor had possession of the recited method of vaccinating a mammal.

Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §102

The Examiner has maintained rejection of Claims 1, 6, 8, 11, 13, 14, 16, and 28- 31under 35 U.S.C. §102(b) as being allegedly anticipated by Dearman et al. (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30). Applicant respectfully disagrees.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "[A]nticipation requires that all of the elements and limitations of the claim are found within a single prior art reference." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

As noted by the Examiner Applicant describes (pgs 22-23) various methods for **penetration** of the stratum corneum (e.g., lipophilic solvents, low frequency ultrasound, electroporation, iontophoresis and intradermal delivery). The referenced discussion in the specification is relevant to various methods of enhancing penetration of antigens through the stratum corneum (see e.g., pg 22, lines 12-15) stating "[a]mong the approaches which have yielded some success in enhancing peptide penetration are included lipophilic vehicles, low frequency ultrasound, electroporation, iontophoresis, and intraepidermal delivery." With the

obvious exception of intraepidermal delivery, these methods permit penetration through intact stratum corneum. This is far different from the recited limitation "**disrupting the stratum corneum**" which is separately defined in the specification. See e.g., pg 10, line 25- pg 11, line 4, stating that "[w]ith respect to immunizing a mammal with an antigen, the term "introducing into" is used to encompass any means of providing the antigen *into* the mammal as distinguished from topical application, i.e. *onto*. For example, the following non-topical routes of administration are deemed to be encompassed by the term "introducing into": parenteral and peroral administration, administration via the gastrointestinal, respiratory and urogenital tracts, **past the protective stratum corneum via injection or mechanical or chemical disruption of the stratum corneum (e.g., intraepidermal, intradermal, subcutaneous, intramuscular, intravascular, intramedullary injection)...**" (emphasis added). Thus, by Applicant's definition, introducing into the mammal excludes topical administration onto the skin—and therefore excludes the cited prior art methods.

Applicant goes on to explicitly distinguish the disruption methods from other non-disrupting, penetration methods (see pg 39, lines 12-21) stating "[t]he antigen could be delivered by penetration of the stratum corneum with needles (as shown in Figures 10-12) or by other commonly used invasive procedures [i.e., disrupting methods]. The antigen(s) can applied topically to the skin or mucous membranes, with (as shown in Figure 9) or without a variety of penetration enhancers, such as but not limited to: chemical or biologic penetration enhancers, and penetration achieved by ultrasound, iontophoresis, electroporation, lasers, thermal effects, hydrostatic pressure or other physical means [i.e., non-disrupting methods]. Alternatively, dendritic cells could be exposed to the antigen(s) by infection or transfection, **or by disruption of the stratum corneum using abrasion, chemical peels, lasers or other physical or chemical means** described in the scientific and patent literature" (emphasis added).

Dearman teaches penetration using a non-disrupting chemical penetration enhancer (DBP in acetone). Thus, contrary to the Examiner's assertion, Dearman does not teach "wherein the antigen or epitope(s) thereof is introduced into the mammal by disrupting the stratum corneum" as that phrase is properly interpreted in view of Applicant's written description. Accordingly, because Dearman does not teach each and every element of Claim 1, Dearman cannot anticipate Claim 1, or Claims 6, 8, 11, 13, 14, 16, 28, 29, 30 and 31, which depend therefrom.

Thus, Applicant respectfully requests withdrawal of the rejections of Claims 1, 6, 8, 11, 13, 14, 16, and 28-31under35 USC §102.

Rejections under 35 U.S.C. §103

The Examiner has maintained rejection of Claims 1, 6, 8, 11, 13, 14, 16, 17, 21, 22, 27-31, and 51 under 35 U.S.C. §103(a) as being allegedly obvious over Dearman et al. in view of Mitragotri et al. (WO 97/04832) and Paul et al. (Vaccine research, 1995, Vol. 4, pp. 145-164). Applicant respectfully disagrees. Under MPEP §2143,

> "[t]o establish a *prima facie* case of obviousness... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure..."

First, as detailed above, Dearman teaches introduction of antigen using a non-disrupting chemical penetration enhancer (DBP and acetone), Mitragotri teaches introduction using non-disrupting application of ultrasound, and Paul teaches introduction using topical delivery of an antigen across the intact skin using submicroscopic transferosome vesicles. Thus, the combination fails to disclose a method of vaccinating "wherein the antigen or epitope(s) thereof is introduced into the mammal by disrupting the stratum corneum" (emphasis added).

Furthermore, the present application is based on a surprising discovery by the inventor that "the application of an effective inducer of Langerhans cell migration is itself a means to induce these cells to capture antigens delivered elsewhere or by other routes, and that might otherwise have little or no immunogenicity. Thus, the effective induction of immature dendritic cell migration and maturation constitutes a potent adjuvant, that can be delivered independently of and separately from delivery of the antigen." (16:21-27).

Currently amended Claim 1 recites that the antigen or epitope(s) thereof is introduced into the mammal by disrupting the stratum corneum and that the topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and in the absence of an antigen inducing dendritic cells to mature and migrate to the draining lymphoid organ. Claim 17 recites that the topical treatment in the absence of an antigen is capable of inducing immature dendritic

cells to mature and migrate to the draining lymphoid organ, wherein introducing said target antigen and administering the treatment are performed independently in any order, and wherein the topical treatment comprises application of ultrasound energy. Independent Claim 51 recites a method for vaccinating a mammal against a target antigen, comprising: "injecting the mammal with an effective dose of said target antigen or an epitope(s) thereof...", which involves disrupting of the stratum corneum.

Dearman discloses that topical DBP in acetone has no influence (Figure 3a, Table 2 lines 1 and 2) on the migration of dendritic cells (DCs) from the skin to draining lymph nodes. Dearman further teaches that DBP is "a chemical that lacks contact allergic potential" (see Dearman p. 24), and is not an antigen because... "[i]n the absence of [an antigen] FITC, application to mice of DBP dissolved in acetone was unable, at any concentration examined, to induce LNC [lymph node cell] proliferative responses" (see Dearman p. 25 and Fig. 1). In the presence of an antigen (FITC), however, Dearman teaches that DBP enhances the permeation and acquisition of antigen (FITC) by dendritic cells (DCs) (see Dearman Table 2 and Fig. 5). Accordingly, one skilled in the art would conclude from a careful review of Dearman that a topic permeation enhancer, like DBP, which lacks contact allergic potential, would fail in the absence of an antigen to induce the maturation and migration of dendritic cells to draining lymphoid organs. In fact, Dearman states that clearly on page 27, lines 3-5: "Administration to mice of acetone containing 10% DBP was without effect on DC accumulation (Fig. 3)" in the draining lymph node.

Furthermore, Dearman fails to teach vaccination against a target antigen, wherein the antigen is introduced into the mammal by disrupting the stratum corneum. Paul teaches vaccinating using non-invasive topical delivery of an antigen across the intact skin using submicroscopic transferosome vesicles. Mitragotri teaches transdermal transport of proteins across intact skin using ultrasound (see page 1, lines 23-25, where ultrasound is suggested as an alternative to invasive procedures). Neither Paul nor Mitragotri teach or suggest introducing the antigen into the mammal by "disrupting" the stratum corneum, as defined in the specification (see detailed citations to the specification above). Indeed, both these secondary references, as well as Dearman, teach methods of introducing antigens, which expressly avoid disrupting the stratum corneum. Thus, because the combination of references fails to teach or suggest all of the

claim limitations, Applicant respectfully asserts that the Examiner has failed to make out a *prima facie* case of obviousness.

Furthermore, all three of these references teach away from introducing an antigen by disrupting a stratum corneum. For example, Dearman suggests that DBP may enhance the immune response to contact hypersensitivity antigens, like FITC, by increasing permeation of the chemical allergen through intact skin. Likewise, as discussed above, both Paul and Mitragotri teach methods designed to avoid disrupting the stratum corneum. Thus, the cited references would teach the skilled artisan to avoid Applicant's recited step of introducing an antigen by disrupting the stratum corneum.

The primary reference of Dearman et al. also fails to teach the use of ultrasound as a topical treatment which in the absence of antigen induces the maturation and migration of immature dendritic cells. Although Mitragotri teaches the use of ultrasound to enhance permeation of proteins through intact skin, Applicant respectfully asserts that one skilled in the art would find neither a motivation to combine the references, nor any expectation of success in coming up with Applicant's claimed invention for the following reasons. The skilled artisan familiar with the teaching of Dearman, would likely conclude that Mitragotri merely teaches an alternate means of enhancing antigen permeation through intact skin—namely ultrasound energy. Mitragotri is silent as to whether ultrasound has any influence on the maturation and migration of dendritic cells to draining lymphoid organs in the presence or absence of antigen. One skilled in the art would infer that ultrasound, like DBP in Dearman, would fail in the absence of an antigen to induce the maturation and migration of dendritic cells to draining lymphoid organs. Thus, the references themselves contain no motivation for the skilled artisan trying to develop a vaccination method to substitute one permeation enhancer for another, since it is the contact hypersensitivity antigen according to Dearman and not the permeation enhancer that causes migration of DCs to draining lymph nodes.

Accordingly, Applicant respectfully requests withdrawal of the §103 rejection of Claims 1, 6, 8, 11, 13, 14, 16, 17, 21, 22, 27-31, and 51 over Dearman in view of Paul and Mitragotri.

The Examiner has maintained the rejection of Claims 1, 18 and 24 under 35 U.S.C. §103(a) as being allegedly unpatentable over Dearman et al. in view of King et al. (Vaccine, 1987, Vol. 5, pp. 234-238).

As discussed above, Claims 1 and 24 are patentable over Dearman in that Dearman fails to teach or suggest a step of introducing the target antigen by disrupting the stratum corneum. Dearman also fails to teach or suggest that the topical treatment is capable in the absence of an antigen of inducing immature dendritic cells to mature and migrate to the draining lymph node. King does not cure these defects, as King teaches an antigen delivery method which avoids disrupting the stratum corneum (i.e., introducing the antigen via the nasal mucosa), and does not suggest additionally topically applying anything to the skin of the intranasally vaccinated patients. Thus, the combination of Dearman and King fails to teach or suggest every element of the claimed invention. Accordingly, Applicant respectfully requests withdrawal of the §103 rejection of Claims 1, 18 and 24 over Dearman in view of King.

The Examiner has maintained the rejection of Claims 19 and 23 under 35 U.S.C. §103(a) as being allegedly unpatentable over Dearman et al. in view of Salyers et al. (Bacterial Pathogenesis, 1994, pp. 8-14 and 144-145).

Currently amended Claim 19 teach that the internal treatment is capable of inducing immature dendritic cells to mature and migrate to the draining lymphoid organ in the absence of an antigen and that said target antigen or epitope(s) thereof is introduced into the mammal by ingestion. Currently amended Claim 23 teach that the topical treatment is capable of inducing immature dendritic cells to mature and migrate to the draining lymphoid organ in the absence of an antigen, and that said target antigen or epitope(s) thereof is introduced into the mammal by via delivery to respiratory, urogenital or gastrointestinal tracts.

As discussed above, Dearman teaches that the function of topically co-applied DBP is to enhance the acquisition of FITC by Langerhans cells in the skin and suggest that the mechanism may be "altered penetration of the allergen through the skin". Salyers teaches that pathogens can penetrate mucosal membranes of gastrointestinal, respiratory and urogenital tracts, which are protected from the pathogens by various types of specialized cells. According to Salyers, the mucus membranes, unlike skin, do not have layers of dead cells and are involved in absorption, and thus cannot be covered by an armor of dead cells as the external skin is. Thus, a person with ordinary skill in the art at the time the invention was made would have concluded based on Dearman that delivery of an antigen through mucosa, i.e. the gastrointestinal, respiratory or urogenital tracts would obviate the need for any other treatment (e.g., DBP to enhance

permeation through the stratum corneum), because the mucosa lacks a stratum corneum and the antigen would have direct access to immature dendritic cells resident in the specialized mucosal-associated lymphoid tissues. Dearman in view of Salyers therefore teaches away from the use DBP in situations wherein the antigen is introduced into a mammal through mucosal membranes.

Furthermore, contrary to the teachings of Dearman, the inventor discovered that exposing immature dendritic cells to a protein or peptide antigen does not induce the maturation and migration of antigen-bearing dendritic cells to draining lymphoid organs (see Figures 11 and 12 of the specification). Only the present invention teaches that there are lipophilic molecules $\leq$500 daltons that in the absence of antigen are able to induce immature dendritic cells to mature and migrate to draining lymphoid organs, thus providing the motivation to use such molecules in conjunction with delivery of an antigen to immature dendritic cells by ingestion.

Dearman fails to suggest to the skilled artisan that lipophilic molecules $\leq$500 daltons are able to induce immature dendritic cells to mature and migrate to draining lymphoid organs in the absence of an antigen (as recited in Claim 19). Salyers does not cure this failure. Therefore, a person with ordinary skill in the art at the time the invention was made would not have been motivated to combine ingestion of antigen with an internal treatment which in the absence of an antigen is capable of inducing immature dendritic cells to mature and migrate to the draining lymphoid organ, as recited in currently amended Claims 19 and 23. Therefore, Applicant respectfully asserts that Claims 19 and 23 are not obvious over Dearman in view of Salyers. Withdrawal of the rejection under §103 is therefore requested.

The Examiner has maintained the rejection of Claims 1, 6, 8, 11, 13-16, 27-31, 52, 53, 55, and 58 under 35 U.S.C. §103(a) as being allegedly unpatentable over Dearman et al. in view of Glenn (US 5,980,898).

Claims 1, 6, 11, 13-16, and 27-31 recite methods for vaccinating a mammal against an antigen comprising *inter alia* introducing the antigen into the mammal by disrupting the stratum corneum. Both independent Claims 55 and 58 recite methods for vaccinating a mammal against an antigen, comprising: injecting (i.e. disrupting stratum corneum) the mammal with an effective dose of the antigen. It is also noted that Claim 55 has the further limitation of "...administering internally to the mammal a treatment... to increase the number of dendritic cells presenting target antigen in a lymphoid organ".

As discussed above, Dearman teaches that dendritic cell acquisition of a contact hypersensitivity antigen can be facilitated by topical coapplication of DBP by increasing permeation of such antigens through intact skin. Glenn teaches a method for vaccinating a mammal comprising the topical administration to intact skin (col. 2, line 53) of an antigen in combination with an activator of DCs, wherein the activator is selected from the lipophilic molecules, trinitrochlorobenzene, dinitrofluorobenzene, pentadecylcatechol and lipid A. Applicant respectfully points out that Lipid A is irrelevant to the present invention because it has a molecular weight of about 1,900 KDa. Trinitrochlorobenzene, dinitrofluorobenzene, and pentadecylcatechol, disclosed by Glenn, have molecular weights $\leq$500 daltons, but are contact hypersensitivity antigens that do not fall within the scope of the recited formulas. Moreover, because trinitrochlorobenzene, dinitrofluorobenzene, and pentadecylcatechol are antigens they clearly do not fall within the limitation of the currently amended Claim 1, as in the absence of an antigen they are incapable of inducing dendritic cells to mature and migrate to the draining lymphoid organ. Dearman teaches that it is the antigen (FITC which is a contact sensitizer) that induces maturation and migration of skin dendritic cells, and that DBP has no effect alone on maturation and migration of dendritic cells. Thus, one skilled in the art would not be motivated to topically administer transcutaneous penetration enhancer DBP alone (without any antigen introduction). Glenn teaches topical administration of lipophilic molecules that are contact hypersensitivity antigens (similar to FITC in Dearman et al.), and thus, consistent with the teaching of Dearman would be expected to induce maturation and migration of dendritic cells. Therefore, as these compounds are antigens just like FITC in Dearman et al., they, according to Dearman, would not require DBP to induce dendritic cells to mature and migrate to the draining lymphoid organ as recited in the currently amended Claim 1.

Claims 52 and 53 recite repeatedly topically administering to the mammal of a lipophilic compound having a molecular weight $\leq$500 daltons, wherein the lipophilic compound is applied in an amount sufficient to increase the number of antigen-bearing dendritic cells presenting said endogenous antigen in a lymphoid organ, wherein said lipophilic compound is selected from the list of formulas and is administered without any added antigen. This, as discussed above, one skilled in the art would not be motivated to topically administer transcutaneous penetration enhancer DBP alone (without any antigen introduction). In conclusion, there is no teaching or

suggestion in either reference to repeatedly administer a lipophilic compound which is itself not an antigen or which is not administered together with an antigen. Moreover, because neither reference teaches repeated topical administration of a lipophilic compound such as DBP (without an antigen), there can be no expectation of successful immunization against an endogenous antigen derived from the references.

Furthermore, neither Dearman nor Glenn teach or suggest a vaccination method in which antigen is introduced into a mammal by disrupting the stratum corneum, the combination fails to set forth a *prima facie* case of obviousness. Indeed, both Dearman and Glenn teach away from methods that include a step of disrupting the stratum corneum—as they are drawn to topical methods of immunization. The Examiner argues that the present Specification does not teach a specific means to "disrupt" the stratum corneum, and further equates various means of transdermal delivery of antigens described in the Specification on page 22, line 19 through page 23, line 29 to the meaning of the word "disrupt". Applicant respectfully disagrees. The dictionary meaning of the word "disrupt" is discussed above. Furthermore, on page 39 of the Specification it is recited that the antigen can be delivered by penetration of stratum corneum with needles or by other commonly used invasive procedures, such as abrasion, chemical peels, lasers , etc. Therefore, the meaning of "disrupting of stratum corneum" recited in the claims does not include ultrasound, electroporation or iontophoresis as clearly supported by the Specification. Accordingly, Claims 1, 6, 8, 11, 13-16, 27-31, 55, and 58 are not obvious over Dearman and Glenn.

In view of the foregoing, Applicant respectfully requests withdrawal of the §103 rejections of Claims 1, 6, 8, 11, 13-16, 27-31, 52, 53, 55, and 58 over Dearman in view of Glenn.

The Examiner maintained the rejection of Claims 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-53, 55, and 58 under the judicially created doctrine of obviousness-type double patenting over claims 1-21 of US patent 6,210,672.

Applicant appreciates the Examiner's acknowledgement that a terminal disclaimer will be filed at the time allowable subject matter is indicated.

CONCLUSION

The Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of the above remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: June 8, 2005

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